PROCEEDING

THE 3rd INTERNATIONAL CONFERENCE ON

PHARMACY AND ADVANCED PHARMACEUTICAL SCIENCES

Book 1:
Pharmaceutical Science & Technology

Faculty of Pharmacy
Universitas Gadjah Mada
Yogyakarta, June 18-19, 2013

Universiteit Utrecht

CYBERJAYA UNIVERSITY
COLLEGE of MEDICAL SCIENCES

Esti Handradi
Fakultas Farmasi Unair

PROCEEDING

The 3rd International Conference on

Pharmacy And Advanced Pharmaceutical Sciences

June 18 – 19, 2013 Yogyakarta, Indonesia

Book 1:

Pharmaceutical Science & Thecnology

Editors:

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Organised By

FACULTY OF PHARMACY
UNIVERSITAS GADJAH MADA

Supported By

Universiteit Utrecht

Published by:
Faculty of Pharmacy Gadjah Mada University
Sekip Utara, Yogyakarta, 55281,
Indonesia

ISBN: 978-602-1594-01-8

First Edition, 2013

Printed in Yogyakarta, Indonesia

Preface From Editor

On behalf of the Editors, I am deeply grateful to all the reviewers who have been working very hard for reviewing manuscripts submitted during the "3rd International Conference on Pharmacy and Advanced Pharmaceutical Sciences" held in Sheraton Hotel Yogyakarta, by the Faculty of Pharmacy, Gadjah Mada University, Yogyakarta, Indonesia on 18 - 19 June 2013.

We would like to acknowledge to keynote speakers and all the distinguished speakers for their valuable contribution during this conference. Furthermore, we also thank the steering committee for their advice and support. Finally, I would appreciate to all participants, paper and poster presenters who participated in the conference as well as cordially contributed by submitting their full manuscripts published in this proceeding.

Finally, we believe that the presence of this proceeding will significantly contribute to the advance scientific research, especially in the field of Pharmaceutical Science and Thecnology.

Yogyakarta, June 2013,
Chief

Abdul Rohman

Welcome to Yogyakarta

Assalamu'alaikum wr wb
Honorable Rector of Universitas Gadjah Mada, Prof. Dr. Praktino, M.Soc.
Honorable our keynote speaker : dr. Boenjamin Setiawan, PhD
Honorable our distinguished invited speakers, our guests, and all participants

First of all, let us praise to the Almighty Allah SWT, because of His Blessing we are able to attend this opening ceremony of the International Conference on Pharmacy and advanced pharmaceutical sciences today.

This morning, it is a great honor for me to welcome you all in this room in our conference. Welcome to Yogyakarta, and we hope you will enjoy your time here. This conference is the third international conference conducted by Faculty of Pharmacy Universitas Gadjah Mada to facilitate the experts meeting and sharing the knowldege among the researchers, academia, college students, policy makers in corresponding fields, and practitioners.
This year, the theme of The 3rd International Conference on Pharmacy and Advanced Pharmaceutical Sciences (ICPAPS 2013) is : **"Pharmaceutical development towards a sustainable and healthy society".** The conference is conducted in collaboration with Utrecht University the Netherland, Nara Institute of Technology Japan, Mahidol University Thailand, and Cyberjaya University, Malaysia. Thank you very much for our international partners.
As a key note speaker in this conference, we are fortunate to have dr. Boenjamin Setiawan, PhD. He is the founder of Kalbe Farma, one of the big pharmaceutical company in Indonesia. His experience in developing pharmaceutical company as a bussinessman as well as his vision in development of medical and pharmaceutical research in Indonesia will be very inspiring, and hopefully will guide us to develop research in our respective fields. We also invited 12 more experts in various field of pharmacy and pharmaceutical sciences, either from Indonesia or overseas, who will give their lectures.
Here, among 300 participants, there are 175 presenters from 10 countries will present their recent research finding, which are divide into two big topics, Pharmaceutical Science and Technology and Clinical and Social Pharmacy. Our high appreciation and sincere gratitude are delivered to all speakers and presenters who enthusiastically participate in our conference.

The organizing commitee deeply acknowledges The Rector of Universitas Gadjah Mada, Nara Institute of Technology Japan, Mahidol University Thailand, and Cyberjaya University, Malaysia, as well as the sponsors for nice collaboration in conducting the conference. As the chairman of the committee, I personally would like to express our high appreciation and gratitude to all team members for the hard work, dedication, and invaluable efforts for the success of the conference.

Finally, we do hope that all participants could get benefit from this event and have enjoyable moment in Yogyakarta.

Wassalamu'alaikum wr wb.

Chairman

Zullies Ikawati

Remark

Dean, Faculty of Pharmacy, Gadjah Mada University

Firstly, let's thanks to Allah who always blesses to all of us, so that we can get together in this wonderful meeting, the 3rd International Conference on Pharmacy and Advanced Pharmaceutical Sciences (ICPAPS 2013). The Faculty of Pharmacy, Gadjah Mada University (GMU) is very happy to welcome all of you ICPAPS 2013 participants in the meeting and also we welcome all of you in Yogyakarta-Indonesia, the home of the Faculty of Pharmacy GMU.

Secondly, we'd like to give a brief introduction of our institution. Faculty of Pharmacy GMU was erected in September 1946, a year after Indonesian Independence, is noted as the oldest Faculty of Pharmacy in Indonesia. Faculty of Pharmacy GMU has been accredited nationally and internationally as well. In addition, collaboration in research, education, social services with several National and overseas Institutions have been established, intended to achieve our goals, one of those is quality of education. Recently, new regulations on Pharmacist roles in Indonesia have been emphasized as health profession, health promoter and pharmaceutical care. Therefore, theme of this ICPAPS 2013 meeting is selected as 'Pharmaceutical developments towards a sustainable and healthy society' that is parallel to those regulations. Faculty of Pharmacy GMU really hopes that this meeting is fruitful for all participants in general and specifically Pharmacy Institutions to develop to improve their education system.

Finally, Faculty of Pharmacy GMU highly appreciates to the Keynote speakers, invited speakers, all participants for spending your time with us, the Committee [Steering Committee, International partners (Universiteit Utrecht-The Netherland, NAIST-Japan, Mahidol University-Thailand, Cyberjaya University-Malaysia) Organizing Committee] who have been working very hard, and last but not least Faculty of Pharmacy GMU thanks to our sponsors for this meeting. Faculty of Pharmacy GMU realizes that without your participation, this meeting never happens.

Sincerely,

Subagus Wahyuono

Rector Speech

Rector, Universitas Gadjah Mada

It gives me genuine pleasure that Universitas Gadjah Mada has the honor of hosting the International Conference on Pharmacy and Advanced Pharmaceutical Sciences, which this year is in its third installment. This Conference, held in collaboration with Japan's Nara Institute of Sciences and Technology, the Netherlands' Universiteit Utrecht, Thailand's Mahidol University and Malaysia's Cyberjaya University, reflects a global commitment maintained by members of prominent think tanks the world over in addressing issues of common concern, which in this year's ICPAPS are Advanced Pharmaceutical Science and Social and Clinical Pharmacy.

Universitas Gadjah Mada, as a leading institution of higher learning in Indonesia, and in its commitment at becoming a World-Class Research University, has long since realized the spinal role of global cooperation in achieving our visions. This is why we welcome any and all effort through which international exchanges of thoughts and expertise can be encouraged. I see this perspective reflected in its entirety in ICPAPS, wherein experts and thinkers from all around the world will gather together and talk of a concerted effort to enhance the quality of pharmacists worldwide, broaden the insights on pharmacy as well as pharmaceutical sciences and technologies, and finally create both a national and international networking system for the dissemination of developments in pharmaceutical sciences and technologies.

Since those are very noble causes we all need to not only address, but also eventually produce into reality, I cannot impress the importance of this Conference for everyone present. Therefore, I can only hope that all the participants, be they researchers, academicians, pharmacists in and outside hospitals, as well as the students, are determined in making the best out of this brief gathering.

I am looking forward to seeing rigorous debates, heated discussions and, most importantly, a result that represents a joint international action held together by scientific truth. Thank you for all your commitment and dedication in organizing and contributing to this conference, and I wish you all the very best of luck.

Prof. Dr. Pratikno, M.Soc. Sc.

Table of Content

PROCESS VALIDATION OF DICLOFENAC SODIUM PATCH MEMBRANE TYPE WITH MENTHOL AS ENHANCER

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ABSTRACT

The aim of this study was to prove that diclofenac sodium patch membrane type with menthol as enhancer have fullfilled the acceptance criteria of process validation. Methods: Diclofenac sodium patch membrane type was prepared by mixing diclofenac sodium as active ingredient with additives such as alginate sodium as drug reservoir, hydroxy propyl methyl cellulose as rate controlling membrane, propilenglicol as plasticizer and menthol as enhancer. The evaluation included organoleptics test, drug content of diclofenac sodium patch in first layer (drug-reservoir), moisture content, homogenity test, drug content of diclofenac sodium patch and drug release. Release of diclofenac sodium by dissolution test, which was carried out using apparatus type 5-paddle overdisk in phosphate buffer pH 7,4 (37 ± 0,5^{0}C, 50 rpm). The process validation was carried out for 3 days with 3 times replication. Result: Fluks of diclofenac sodium release about 3,866 ± 0,004. From the overall results of test showed that CV <6% and one way ANOVA analysis showed no significant difference of diclofenac sodium patchs were performed on 3 different days with 3 times replication. Conclusion: Process of manufacturing of diclofenac sodium patch membrane type with menthol as enhancer has been validated.

Key words: process validation, diclofenac sodium, patch, membrane type, menthol

INTRODUCTION

Inflammation is tissue vascularisation reaction because of injury. In general, inflammation gives discomfort and are considered harmful to the patient (Singh *et al.*, 2011). Diclofenac sodium is a NSAID drug that has anti-inflammatory, analgesic and antipyretic effect and has high therapeutic index compared to other NSAID. Diclofenac sodium is absorbed 100% after oral administration, but only 60% of drug that reaches systemic circulation due to first-pass metabolism. Additionally diclofenac sodium have gastric irritation effect on oral route (Chuasuwan et al, 2008). To avoid this problems, the transdermal route can be alternative option for this drug. One of the dosage form of transdermal is patch. Patch is a dosage form that designed to deliver drug through the skin. In membrane systems, patch has a separate drug layer in solution, suspension, gel form or dispersed in the matrix polymer between backing layer and rate controlling membrane that can produce zero-order release rate (Bajaj *et al*, 2011). In this research, I choose membrane type patch because it can provide better rate control of delivery and has initial burst in drug release (Margetts and Sawyer, 2007).

In a previous study, in vitro test of patch showed well drug release (Pujianti, 2006). Significant changes to the process that can affect the quality of the product have to be validated (BPOM, 2006). Therefore, it is necessary to ensure that the validation process for manufacturing of sodium diclofenac patch will consistently produce a product that conforms to predetermined specifications.

METHODOLOGY

Instrument

The instrument used in this research include analytical balance, Scanning Electron Microscope (SEM), UV Visible Spectrophotometer , oven, magnetic stirer, SCHOTT GLAS mainz pH meter CG 842 type, series of instrument for penetration percutan testing ERWEKA DT 700, cell diffusion, desiccator and glass.

Material

The main materials used in this research is pharmaceutical grade. These materials include diclofenac sodium (Aarti Drugs Limited), sodium alginate (Sigma-Aldrich), HPMC E15 (ILE Pharmaceutical), propylene glycol (Bratachem), menthol (Bratachem), ethanol 96% (Bratachem) and distilled water.

Manufacturing Patch

1. Manufacture of drug reservoir patch

0,1 g Diclofenac sodium dissolved with 11 mL mixture of water: ethanol 80:20 using stirrer 500 rpm for 5 minutes, then add 5,232 g sodium alginate 9% and stirring constantly with a stirrer 500 rpm for 10 minutes. The resulting mixture is divided into 3 dosage of each patch and weighed 3,967 g then poured on the backing membrane. Mixed drug-reservoir is then dried at temperature at 45° C for 1 hour to form a semi-dry matrix. Patch then tested drug content of diclofenac sodium in first layer (mixture drug- reservoir).

2. Manufacture of rate controlling membrane

5,12 g HPMC E15 20% was added 0.213 g propylene glycol and stirring constantly using a stirrer 500 rpm for 10 minutes. 0,106 g Menthol dissolved in ethanol and added to the mixture, stirring constantly with a stirrer 500 rpm for 5 min. The mixture was then poured on drug reservoir and dried at temperature of 40 ° C for 2 hours. Patches then tested organoleptic, surface homogeneity assay, homogeneity of dosage form, moisture content, drug content and release drug. The validation process is carried out for 3 days, each with 3 times replication. Formulation of diclofenac sodium patch with menthol as enhancer can be seen in table 1.

Table 1. Formulation of diclofenac sodium *patch* membran type

Material	Function	Weight (mg) / 7,065 cm^2	
		Control	Formula
Diklofenac sodium	Bahan aktif	14	14
Alginat sodium 9%	*Drug reservoir*	736	736
HPMC E15 20%	*Rate-controlling membrane*	720	720
Propilenglicol	*Plastisizer*	30	30
Menthol	*Enhancer*	-	15
Total		1500	1515

Statistical analysis

Drug content in first layer (drug-reservoir), moisture content, drug content in the patch and drug release of diclofenac sodium in validation process are analyzed using program SPSS (Statistical Package for the Social Sciences) 17 by one-way analysis of variance (ANOVA).

RESULTS AND DISCUSSION

Validation process is intended to provide assurance that the preparation process will consistently produce a product according to predetermined specifications (Nash and Wachter, 2003). Before performed validation process,

facilities, systems and equipment used must have been qualified and analytical methods must be validated (BPOM, 2006).

Maximum Wavelength and standard curve result

The maximum wavelength (λ) of diclofenac sodium was 276 nm at absorbance 0,450. Standard curve can be seen in this table. From data analysis obtained regression equation for standard curve was y = 0.032 x - 0.007 with a correlation coefficient (r) = 0.99997. This is indicates that there is a linear relationship between absorption and diclofenac sodium levels so can be used as a curve standard.

Drug content in first layer

Drug content in first layer of sodium diclofenac patch membrane type with menthol as enhancer can be seen in table 2. Content of sodium diclofenac were in the range 98-102% and CV on each day <6%. Based on one-way ANOVA test found that there was no significant difference (p = 0,347) content of sodium diclofenac membran type patch in manufacturing 3 different days with each of three replication.

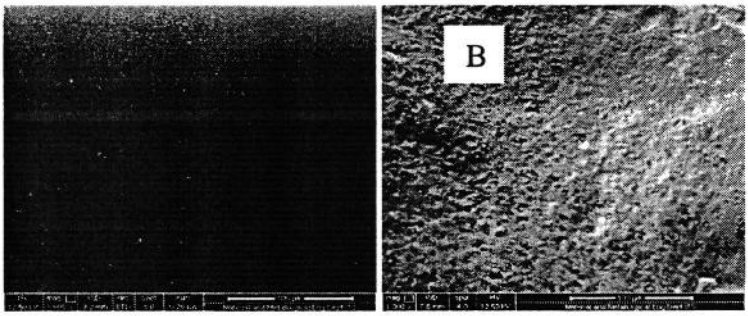
Organoleptic Assay

Organoleptic assay's result of diclofenac sodium patch membrane type with menthol as enhancer is a patch has a round shape, thin and smooth surface; translucent brownish color and smelling menthol. Based on the results of organoleptic test was found that there was no difference organoleptic in the manufacture of sodium diclofenac patch on 3 different days.

Surface homogeneity assay

Result of surface homogeneity sodium diclofenac patch using a Scanning Electron Microscope (SEM) with a magnification of 1000 x can be seen in picture 1. This picture indicating that the addition of menthol resulted in visible surface patch elicits a uniform distribution on the surface of diclofenac sodium patch.

A



Picture 1. Surface homogeneity of diclofenac sodium patch using Scanning Electron Microscope (SEM) with a magnification of 1000 x. A: Patch diclofenac sodium type membranes without menthol B: Patch diclofenac sodium with menthol as enhancer.

Moisture Content Assay

The results of the percentage average moisture content diclofenac sodium patch can be seen in table 2. The percentage of moisture content obtained were in the range 10-15%. Percentage CV obtained on each day of <6%. Based on one-way ANOVA test found that there was no significant difference (p = 0,586) percentage of

moisture content of diclofenac sodium patch membrane type by making the patch on 3 different days with each of the three replication.

Table 2. Assay of Validation process

Assay	Day	% Average ± SD	CV (%)
Drug content in first layer	I	99,28 ± 0,30	0,31
	II	99,07 ± 0,19	0,19
	III	98,88 ± 0,39	0,40
Moisture Content	I	12,28 ± 0,33	2,68
	II	11,94± 0,33	2,78
	III	12,27± 0,59	4,79
Drug Content	I	98,89 ± 0,29	0,29
	II	98,50 ± 0,33	0,34
	III	99,06 ± 0,50	0,50
Fluks of release	I	3,866 ± 0,004	0,10
	II	3,862 ± 0,004	0,10
	III	3,865 ± 0,005	0,13

Drug Content

Drug content of diclofenac sodium patch were in the range 98-102% and CV obtained on each day of <6%. Based on one-way ANOVA test found that there was no significant difference (p = 0,278) content of diclofenac sodium membran type patch in manufacturing 3 different days with each of three replication.

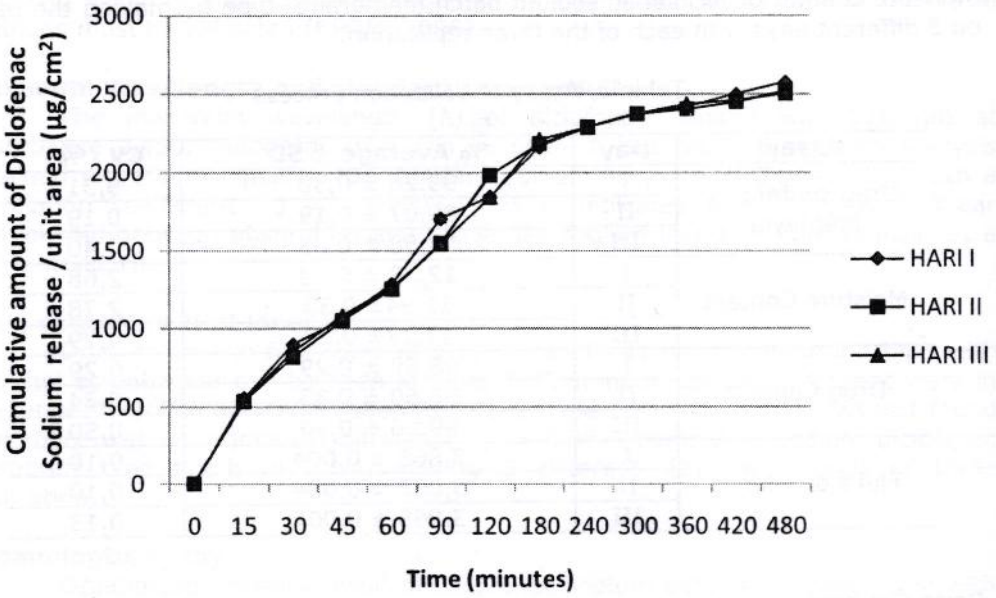
Drug Release

Data cumulative amount and profil of diclofenac sodium patch release can be seen in table 3 and picture 2. Data is cumulative amount of diclofenac sodium patch with 3 times the replication ± SD. From data of release, is make linear regression equation between time (minutes) versus the cumulative amount of diclofenac sodium (µg / cm^2) were released from the minute 0-480. Flux value is the slope of the regression equation.

Table 3 Cumulative amount of Diclofenac sodium patch release with 3 times replication

Waktu	Hari I	Hari II	Hari III	KV (%)
0	0,000 ± 0,000	0,000 ± 0,000	0,000 ± 0,000	0,00
15	553,211 ± 11,211	532,421 ± 9,675	538,342 ± 6,814	1,98
30	896,281 ± 4,683	815,805 ± 20,653	847,806 ± 10,255	4,75
45	1053,884 ± 4,772	1052,156 ± 7,995	1082,990 ± 5,702	1,63
60	1284,346 ± 4,044	1254,360 ± 8,153	1260,964 ± 7,994	1,24
90	1703,622 ± 21,262	1546,212 ± 11,483	1539,493 ± 17,048	5,82
120	1840,728 ± 1,429	1981,376 ± 32,729	1840,014 ± 13,730	4,31
180	2161,932 ± 2,637	2182,829 ± 24,832	2210,302 ± 14,257	1,11
240	2289,892 ± 2,663	2288,708 ± 19,227	2288,955 ± 12,784	0,03
300	2376,545 ± 2,689	2375,360 ± 8,896	2371,898 ± 5,088	0,10
360	2416,262 ± 6,649	2405,412 ± 0,885	2436,120 ± 4,391	0,64
420	2498,528 ± 7,220	2451,151 ± 8,397	2461,354 ± 6,196	1,01
480	2574,698 ± 2,728	2519,425 ± 9,486	2501,480 ± 14,332	1,51

Data is cumulative amount of diclofenac sodium patch with 3 times the replication ± SD



Picture 2. Profil of diclofenac sodium patch release

Drug release is performed to determine the amount of drug released from the base. At delivery patch, the drug is in high concentration.. Because of the high concentration in the patch and the presence of low concentrations in the blood, then drug will diffuse continuously to maintain a constant concentration of drug in the circulation (Bajaj et al, 2011). Process of drug transport through barrier constituted by Fick's first law, namely the number of molecules of compounds that pass through each unit barrier in each unit of time expressed as a fluks (J) (Martin, 1993)

Percentage CV of fluks sodium diclofenac were obtained on each day of <6%. Based on one-way ANOVA test found that there was no significant difference ($p = 0.461$) fluks of diclofenac sodium patch release by making the patch on 3 different days with each of the three replication.

Homogeneity of dosage form

Preparation homogenity test of sodium diclofenac, patch is divided into 4 sections. The results of homogeneity test of diclofenac sodium patch membrane type with menthol enhancer can be seen in table 4. Based on one-way ANOVA test found that there was no significant difference ($p = 0.777$) content of diclofenac sodium patch membrane type with menthol as enhancer by making the patch on 3 different days with each of the three replication. Percentage CV obtained on each day of <6% so it can show that the content of diclofenac sodium patch membrane type has been spread homogeneous in surface of patch.

Table 4. Results of homogeneity test of diclofenac sodium patch membrane type with menthol enhancer

Day	Replication	Average drug content (%) ±SD	CV (%)
I	1	99,86 ± 0,73	0,73
	2	99,31 ± 0,84	0,84
	3	99,45 ± 0,86	0,87
II	1	99,16 ± 0,73	0,73
	2	99,28 ± 1,12	1,13
	3	99,45 ± 1,54	1,55
III	1	99,64 ± 1,13	1,13
	2	99,53 ± 0,72	0,71
	3	99,38 ± 1,12	1,12

From the overall results of test showed that CV <6% and one way ANOVA analysis showed no significant difference of diclofenac sodium patchs were performed on 3 different days with 3 times replication.

Conclusion

The process of manufacture of sodium diclofenac patch membrane type with menthol as enhancer has been validated

Acknowledgments

Thanks to DIKTI on a research grant awarded for this research as well as other participan.

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